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Food and Drug Administration  
Rockville MD 20857

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Marvin J. Garrett  
Vice President, Regulatory Affairs and  
Quality Assurance & Compliance  
ISTA Pharmaceuticals, Inc.  
15295 Alton Parkway  
Irvine, CA 92618

Re: Docket No. 2005P-0134/CP1

Dear Mr. Garrett:

This letter responds to the citizen petition dated April 6, 2005 (Petition) that you submitted on behalf of ISTA Pharmaceuticals, Inc. (ISTA). In the Petition, you request that the Food and Drug Administration (FDA or the Agency) reverse its decision to grant ISTA a 5-year period of marketing exclusivity for its naturally sourced hyaluronidase product, Vitrase (NDA 21-640), under section 505(c)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) (21 U.S.C. 355(c)(3)(E)(ii)), previously section 505(c)(3)(D)(ii) of the Act. You ask that FDA, instead, grant ISTA a 3-year period of marketing exclusivity for this product under section 505(c)(3)(E)(iii) of the Act, previously section 505(c)(3)(D)(iii).

We have carefully considered the issues you raise in your petition as well as the comments submitted by Amphastar Pharmaceuticals, Inc., and ISTA's response to them. For the reasons stated below, your petition is denied.

### **I. Summary**

Your petition discusses the appropriate application of certain exclusivity provisions added to the FDCA as part of the 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman amendments). Briefly stated, the Act provides that if FDA approves a drug product that does not contain a previously approved *active ingredient* (including any ester or salt of the *active ingredient*), the product is granted 5-year marketing exclusivity. Among other things, this exclusivity prevents FDA from accepting (generally for 5 years) a subsequent application that refers to that drug and relies on safety and efficacy data that the subsequent applicant did not develop and to which it has no right of reference (i.e., an application submitted in accordance with section 505(b)(2) of the Act) (see 21 U.S.C. 355 (b)(2) and (c)(3)(E)(ii)).

The statute further provides that if FDA approves an application for a drug product that contains a previously approved active ingredient (including any ester or salt of the active ingredient) (*active moiety*)<sup>1</sup> and that application includes new clinical investigations essential to the approval

<sup>1</sup> By regulation, FDA has interpreted *active ingredient* (including any ester or salt of the active ingredient) (21 U.S.C. 355(c)(3)(E), 355(j)(5)(F)) to mean *active moiety* (21 CFR 314.108(a)).

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of the application and conducted or sponsored by the applicant, the application will be granted 3-year marketing exclusivity. Among other things, this exclusivity prevents FDA from approving a 505(b)(2) application for 3 years for the same conditions of approval (see 21 U.S.C. 355(b)(2) and (c)(3)(E)(iii)).<sup>2</sup>

To make an exclusivity determination for ISTA's Vitrase, the Agency had to resolve a novel regulatory question that arose in an unusual factual context. The general question raised is what exclusivity to grant a drug product if the Agency does not have sufficient information to determine whether the drug contains a previously approved active moiety. That is, should the Agency treat such a drug product as (1) containing a previously approved active moiety (thereby making the product eligible for 3-year exclusivity) or (2) not containing a previously approved active moiety (thereby making it eligible for 5-year exclusivity)? This question is presented in the context of recent approvals of hyaluronidase drug products.<sup>3</sup>

To resolve this issue, the Agency considered, among other things, the nature and amount of data that generally would be necessary to support approval of different types of drug products. To support approval of a drug product the Agency knows does not contain a previously approved active moiety, an applicant generally would be required to submit substantial clinical safety and efficacy data. To support approval of a product for which the Agency has insufficient information to know whether it, in fact, contains a previously approved active moiety, an applicant typically would have to satisfy comparable clinical data requirements. Therefore, in light of what could reasonably be expected to be comparable data requirements for these two categories of products, the Agency has decided it is appropriate to treat them equivalently for purposes of marketing exclusivity as well.

A drug product known not to contain any previously approved active moiety receives 5-year marketing exclusivity. Accordingly, the Agency has concluded that 5-year marketing exclusivity should also apply to products about which the Agency has insufficient information to know whether they contain a previously approved active moiety. Therefore, the Agency has decided under the circumstances before us (1) to apply a presumption for purposes of marketing exclusivity that a product does not contain a previously approved active moiety if the Agency has insufficient information to know if, in fact, it contains one, and (2) to grant 5-year marketing exclusivity to Vitrase in accordance with this presumption.

The regulatory status of Vitrase, and other hyaluronidase products approved for the same uses, is unusual. The hyaluronidase in these products is not fully characterized (and thus the Agency does not know whether these products, in fact, contain any previously approved active moieties). Consequently, FDA granted Vitrase 5-year marketing exclusivity in accordance with the

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<sup>2</sup> Section 505(j)(5)(F) of the Act, previously section 505(j)(5)(D), establishes equivalent marketing exclusivity provisions delaying FDA action on abbreviated new drug applications (ANDAs).

<sup>3</sup> To answer this petition, FDA does not need to address the possible scope of 3-year marketing exclusivity under section 505(c)(3)(E)(iii) if that exclusivity were applicable rather than 5-year exclusivity. Accordingly, we do not discuss your interpretation of that provision.

presumption.<sup>4</sup> However, naturally sourced mammalian testicular hyaluronidase drug products have been legally marketed for over 50 years for their three currently approved indications (i.e., as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents); an in vitro assay is available that can reliably demonstrate efficacious activity of particular hyaluronidase products for these indications; and the safety and efficacy of hyaluronidases for their currently approved drug uses are well understood. As a result of these unusual circumstances, the data requirements for approval of Vitrase and similar hyaluronidase products for these uses are relatively modest. The Agency requires only a limited clinical study of allergenicity.<sup>5</sup>

You argue that the Agency does not have the discretion to interpret the Act such that 5-year exclusivity applies to Vitrase because Vitrase was approved under a section 505(b)(2) application. You argue that such an application would not have been approved unless Vitrase contained a previously approved active ingredient, which you argue would make 5-year marketing exclusivity unavailable. As explained in subsection IV.B, however, there is no requirement that section 505(b)(2) applications be permitted only for products containing previously approved active ingredients. You also argue that the presumption would lead to confusion and provide meaningless protection. We disagree. The circumstances in which the presumption applies depend on the specific characteristics of the drug product. The exclusivity granted blocks approval of any subsequent drug product shown to contain an active moiety present in the product entitled to the exclusivity. Further, application of the presumption, including to Vitrase, promotes pharmaceutical competition without inhibiting innovation, consistent with the objectives of the Hatch-Waxman amendments.

FDA has adopted and applied a permissible and appropriate statutory construction, a course of action well within the Agency's discretion as the authority responsible for implementing the FDCA. FDA has adopted this position after careful consideration of the facts, applicable law, and policy.

## **II. Background on Hyaluronidase and the Vitrase Approval**

Mammalian testicular hyaluronidase products have been legally marketed for over 50 years. The efficacy of hyaluronidase for injection USP, and hyaluronidase injection USP, for the three indications identified above was established through FDA's Drug Efficacy Study Implementation (DESI) process (see letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research (CDER) to Kent S. Allenby, M.D., F.A.C.P., Vice President,

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<sup>4</sup> As discussed in section IV.C, the Agency has also granted 5-year marketing exclusivity to Amphastar's hyaluronidase product, Amphadase, in accordance with the presumption.

<sup>5</sup> Answering this petition does not require FDA to consider approval requirements for recombinant hyaluronidase products. Accordingly, the Agency takes no position in this response regarding such requirements, and we do not address your views on them.

Clinical Research and Medical Affairs, Baxter Healthcare Corporation (May 5, 2004) (Docket 2003P-0494) (Response to the Baxter Petition)). The Agency's conclusions regarding the DESI reports for hyaluronidase were published in the *Federal Register* on September 23, 1970 (35 FR 14800-1).

The Agency stated in the Response to the Baxter Petition that, except for product-specific allergenicity, it considers mammalian testicular hyaluronidases safe for their currently approved drug uses, based on available literature and a review of adverse event reports showing very few adverse events for hyaluronidase from various sources and in various formulations. The Agency also stated that it considers a current *United States Pharmacopoeia* (USP) in vitro assay for enzymatic activity of hyaluronidase sufficient to demonstrate the efficacy of specific hyaluronidase products for the three currently approved indications.<sup>6</sup> As a result of this combination of data, experience, and test methods, the only clinical data the Agency has required to support marketing of hyaluronidase products for their currently approved drug uses have been product-specific clinical allergenicity data (required only if human safety data are otherwise unavailable for the specific product).<sup>7</sup>

At one time, there were ten legally marketed hyaluronidase products with new drug applications (NDAs). The last of these, Wyeth's Wydase, was withdrawn from the market in December 2001. FDA approved 505(b)(2) applications for ISTA's (ovine sourced) Vitrase on May 4, 2004, and Amphastar's (bovine sourced) Amphadase on October 26, 2004. Because of the unusual circumstances discussed above, neither ISTA nor Amphastar had to submit any clinical data other than limited, product-specific allergenicity data to support marketing of their respective products.

In September 2004, FDA informed ISTA that it had received 3-year marketing exclusivity for Vitrase. In October 2004, FDA notified ISTA that the Agency was changing its exclusivity determination and, instead, was granting ISTA 5-year marketing exclusivity for Vitrase. FDA explained that "After reviewing information and data regarding hyaluronidase drug products, which are protein products that have not been fully characterized, the Agency has decided that 5-year exclusivity is appropriate because we have inadequate information to determine whether any active moiety in Vitrase is the same as any previously approved active moiety" (letter from Jonca C. Bull, M.D., Director, Office of Drug Evaluation V, CDER, FDA, to Marvin J. Garrett, ISTA Pharmaceuticals, Inc. (October 2004 Letter)).

As explained in the October 2004 Letter, FDA changed its view on the appropriate exclusivity for ISTA's mammalian testicular sourced hyaluronidase product after reviewing the available information on the specific structural characteristics of hyaluronidases. Naturally occurring hyaluronidase products have never been fully characterized with respect to the chemical structure of the pharmacologically active enzymes or to impurities. The USP monograph for hyaluronidase drug products describes them only as "dry, soluble enzyme products prepared

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<sup>6</sup> Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 26.

<sup>7</sup> For further discussion of hyaluronidase, including its safety and effectiveness, see the Response to the Baxter Petition.

from mammalian testes" and capable of certain activity.<sup>8</sup> The 1970 DESI findings established efficacy for certain marketed products containing mammalian hyaluronidases without further describing their active ingredients or defining the species source for the testicular material.<sup>9</sup>

At this time, the Agency has no information showing that any hyaluronidase products have been adequately characterized to enable the Agency to determine whether they contain a previously approved active moiety. The Agency understands, based upon its review of literature and other information, that the amino acid sequence of hyaluronidase molecules varies based both on the species and the tissue from which they are sourced. It is also known that the amino acid sequence for hyaluronidase enzymes extracted from a particular type of tissue from the same species may vary (i.e., there may be a single type of hyaluronidase molecule or multiple types of hyaluronidase molecules extracted from the same type of tissue from the same species). In addition, the types of hyaluronidase molecules present may vary from batch to batch for a given drug product.<sup>10</sup>

Because of this uncertainty, although the Agency can determine whether a naturally sourced hyaluronidase product contains a member of a class of pharmacologically active enzymes (i.e., of a category of hyaluronidases), the Agency cannot determine the specific enzyme or enzymes contained in any naturally sourced hyaluronidase product (i.e., the structure of the precise molecule or molecules responsible for the pharmacological activity of the drug).

### **III. Statutory and Regulatory Authorities**

#### **A. Section 505(b)(2) Applications**

Section 505(b) of the Act establishes the approval requirements for NDAs. To be approved, an application submitted under section 505(b) must be supported by investigations showing the drug product to be safe and effective (21 U.S.C. 355(b)(1)). One pathway under section 505(b)

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<sup>8</sup> Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 26.

<sup>9</sup> Briefing letter, Department of Health, Education, and Welfare, from Henry E. Simmons, M.D., to Charles C. Edwards, M.D., Commissioner of Food and Drugs, DESI announcement 6343: Hyaluronidase, August 11, 1970.

<sup>10</sup> See, e.g., Zaneveld, J.D., K.L. Polakoski, and G.F. Schumacher, 1973, Properties of Acrosomal Hyaluronidase from Bull Spermatozoa: Evidence for Its Similarity to Testicular Hyaluronidase, *J of Biol Chem*, 248(2):564-570; Csoka, A.B., G.I. Frost, T. Wong, and R. Stern, 1997, Purification and Microsequencing of Hyaluronidase Isozymes from Human Urine, *FEBS Lett*, 417(3):307-310; Fiszer-Szafarz, B., A. Litynska, and L. Zou, 2000, Human Hyaluronidases: Electrophoretic Multiple Forms in Somatic Tissues and Body Fluids: Evidence for Conserved Hyaluronidase Potential N-glycosylation Sites in Different Mammalian Species, *J of Biochem Biophys Methods*, 45(2):103-116; Oettl, M., J. Hoechstetter, I. Asen, G. Bernhardt, and A. Buschauer, 2003, Comparative Characterization of Bovine Testicular Hyaluronidase and Hyaluronate Lyase from *Streptococcus Agalactiae* in Pharmaceutical Preparations, *Eur J of Pharm Sci*, 18(3-4):267-277.

In light of the DESI findings, literature and information derived from marketing history for hyaluronidase products, differences such as these would not be expected to have an effect on safety or effectiveness when the drug product meets the requirements for tissue source, in vitro activity and allergenicity potential discussed in the Response to the Baxter Petition.

provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference. For purposes of this discussion, we refer to these applications as *stand alone* NDAs. The amendments made to the FDCA by the Hatch-Waxman amendments provided an alternate approval pathway, by adding a new subsection, 505(b)(2), to the Act.

Section 505(b)(2) provides for approval of an application submitted under section 505(b)(1):

for a drug for which the [safety and efficacy] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c). As for any application submitted under section 505(b)(1), a 505(b)(2) application must satisfy the statutory requirements for safety and effectiveness information. However, the Agency has interpreted section 505(b)(2) to authorize applicants to support the safety and/or effectiveness of the drug product either with published reports of studies to which the applicant has no right of reference, or with an Agency finding of safety and effectiveness for a previously approved drug product, to the extent reliance on such reports or findings is scientifically justified. A 505(b)(2) application often describes a drug product with substantial differences from a drug product previously approved by FDA. These differences may include, for example, a change of active ingredient, dosage form, indication, or route of administration.<sup>11</sup> Accordingly, a 505(b)(2) application must support those differences with appropriate safety and effectiveness information.<sup>12</sup>

## **B. Five-Year Marketing Exclusivity**

The Hatch-Waxman amendments provide for the granting of 5-year marketing exclusivity to qualified drug products approved under a section 505(b) application. This exclusivity protects them from competition from certain products described in sections 505(b)(2) and 505(j). This exclusivity does not block acceptance and review of stand alone NDAs (supported entirely by data developed by the applicant or to which the applicant has a right of reference).

Five-year marketing exclusivity with respect to 505(b)(2) applications is provided for in section 505(c)(3)(E)(ii) of the Act, which states in pertinent part that:

If an application submitted under [505(b)] for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been

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<sup>11</sup> See 21 CFR 314.54(a); Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganlaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, PhD, Vice President Regulatory Affairs, Biotechnology Industry Organization, William R. Rakoczy, Esq., Lord, Bissell & Brook LLP 19-21 (Oct. 14, 2003) (docket nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1) (505(b)(2) Response).

<sup>12</sup> See the 505(b)(2) Response for additional information on the 505(b)(2) approval pathway.

approved in any other application under [505(b)], is approved . . . no application which refers to the drug for which the [505(b)] application was submitted and for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use . . . may be submitted under subsection (b) before the expiration of five years from the date of approval of the [505(b)] application . . . .

Briefly stated, this provision grants a marketing exclusivity, generally of 5 years,<sup>13</sup> to a drug approved under a section 505(b) application that contains no active ingredient (including any ester or salt of the active ingredient) previously approved by the Agency. During this exclusivity period, no subsequent 505(b)(2) application referring to the drug may be submitted to FDA for marketing approval.<sup>14</sup>

### C. New Chemical Entities (NCEs) and Active Moieties

The implementing regulations for section 505(c)(3)(E) (and 505(j)(5)(F)) of the Act refer to drug products qualifying for 5-year marketing exclusivity as *new chemical entities* (NCEs) (see 21 CFR 314.108). The regulations define an NCE as "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [A]ct" (21 CFR 314.108(a)). *Active moiety*, in turn, is defined as:

[T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

(Id).

In short, FDA has long interpreted *active ingredient (including any ester or salt of the active ingredient)*, as used in section 505(c)(3)(E) of the Act, to mean *active moiety*. As reflected in the preamble to the 1989 proposed rule on ANDA regulations and 1994 final rule on ANDA regulations and patent and exclusivity provisions, the Agency believes this reading is consistent with the legislative intent "not to confer significant periods of exclusivity on minor variations of

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<sup>13</sup> An applicant can submit a 505(b)(2) application after 4 years if the applicant opts to include in its application a certification of its belief that a patent, listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) as claiming either the drug for which the investigations were conducted or a use of that drug for which the applicant is seeking approval, is invalid or would not be infringed by the proposed drug product (21 U.S.C. 355(c)(3)(E)(ii)).

<sup>14</sup> This exclusivity protects the active moiety, delaying Agency action on 505(b)(2) applications for drug products containing the same active moiety, regardless of whether these products differ from the drug granted exclusivity in other respects, such as indication, dosage form, or route of administration. The exclusivity available under section 505(j)(5)(F)(ii) similarly operates to delay Agency action on 505(j) applications for drugs containing the same active moiety.

previously approved chemical compounds" (54 FR 28872 at 28898; see 54 FR 28872 at 28897-28898 (July 10, 1989), 59 FR 50338 at 50357-50358 (Oct. 3, 1994), and *Abbott Labs. v. Young*, 920 F.2d 984 (D.C. Cir. 1990)).

In making exclusivity determinations for drug products approved under section 505(b) of the Act, the Agency seeks to identify the molecule or ion responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108). One criterion is the molecule's covalently bonded structure. The amino acids of a protein are covalently bonded to one another. Accordingly, in assessing the structure of a protein molecule (such as a hyaluronidase enzyme) for exclusivity purposes, the Agency considers the amino acid sequence of the protein. In the absence of more extensive data identifying the amino acid sequence of any hyaluronidase enzyme, we cannot determine whether, in fact, any hyaluronidase product contains the same active moiety included in a previously approved drug product, which is why we are applying a presumption as explained in section IV.

#### **IV. Presumption of NCE Status Is Permissible for Hyaluronidase**

As explained in the October 2004 Letter to ISTA, FDA has concluded that ISTA's Vitrase qualifies as an NCE and is therefore entitled to 5-year marketing exclusivity. We arrived at this conclusion because Vitrase contains naturally sourced hyaluronidases, the amino acid sequences of which have not been fully determined. As a result, the Agency cannot determine whether Vitrase contains a previously approved active moiety. The Agency believes it is permissible under the Act and appropriate from a policy perspective to presume that a product is an NCE if FDA cannot determine whether the product contains a previously approved active moiety.

Five-year marketing exclusivity applies if a product does not contain an active moiety that has been previously approved, and 3-year marketing exclusivity applies if the product contains a previously approved active moiety and the application contains new clinical studies (other than bioavailability studies), essential to approval, conducted by or for the applicant.<sup>15</sup> The Act and the Agency's regulations are silent as to which marketing exclusivity is appropriate if a product has not been sufficiently characterized to allow the Agency to determine whether any active moiety the product contains has been previously approved (making 3-year exclusivity available)

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<sup>15</sup> Section 505 of the Act states that:

If an application submitted under [505(b)] for a drug, *which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under [505(b)]*, is approved after the date of the enactment of this clause and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under [505(b)] for the conditions of approval of such drug in the approved [505(b)] application effective before the expiration of three years from the date of the approval of the application under [505(b)] if the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted (emphasis added).



or not (making 5-year exclusivity appropriate). The Agency has not previously expressly considered how to apply the Act in these circumstances.<sup>16</sup>

Generally, if the Agency has insufficient information to know whether a product contains a previously approved active moiety, the applicant would be required to submit an NDA containing substantial clinical safety and efficacy data. These data requirements could reasonably be expected to be comparable to those that would be needed for approval of an NCE.<sup>17</sup> Under the presumption, if it is not known whether a product contains a previously approved active moiety, the product also would be treated as an NCE for marketing exclusivity purposes, and, accordingly, granted 5-year exclusivity.

You assert that the presumption in favor of NCE status is not permissible under the Act on the grounds that the active ingredient in Vitrase has been previously approved. You arrive at this conclusion through the following line of argument: (1) the term *active ingredient* means a therapeutically active component of a drug product; (2) to approve Vitrase under section 505(b)(2) of the Act, the Agency had to determine that Vitrase includes a previously approved active ingredient; and (3) how fully characterized the active ingredient may be is, therefore, irrelevant to the marketing exclusivity determination. However, this definition of active ingredient is not apposite as explained in section IV.A, and the assertion that 505(b)(2) applications cannot be submitted for previously unapproved active ingredients is incorrect as explained in section IV.B. You also argue that the presumption will produce meaningless exclusivities and confusion. However, we believe, as explained in section IV.C, the exclusivity is not meaningless and confusion need not arise from application of the presumption. In addition, the effects of applying the presumption are consistent with the objectives of the Hatch-Waxman amendments: to foster both innovation and competition in the pharmaceutical marketplace.

**A. Agency Interpretation of Active Ingredient (Including Any Ester or Salt of the Active Ingredient) Is Permissible**

As you note, FDA has consistently interpreted the term *active ingredient (including any ester or salt of the active ingredient)* for purposes of section 505(c)(3)(E) (and 505(j)(5)(F)) of the Act to

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<sup>16</sup> An alternative to adopting a presumption might have been to not make any exclusivity determination at this time because of the absence of data to determine as a factual matter whether any hyaluronidase product contains a previously approved active moiety. Without taking a position on the permissibility of that alternate interpretation, having considered the matter, we believe that a presumption in favor of NCE status, and a consequent grant of 5-year marketing exclusivity, is both permissible and appropriate. As this response explains, FDA sees no statutory bar to granting 5-year exclusivity on the basis of a presumption in favor of NCE status, and the Agency believes application of this presumption comports with the objectives of the Hatch-Waxman amendments.

<sup>17</sup> As discussed in Section II, due to the availability of certain safety and effectiveness information and the in vitro assay, only limited clinical data on allergenicity are required for approval of certain hyaluronidases for their currently approved drug uses. These clinical data requirements are not as substantial as those that generally would apply to a product the Agency knows contains no previously approved active moiety. However, the specific data requirements are appropriate in light of the unusual characteristics of these products. Regardless, a presumption of NCE status is permissible and, as discussed in section IV.C, its application to these hyaluronidase products is consistent with the objectives of the Hatch-Waxman amendments.

mean *active moiety*. In the context of this section, we believe this interpretation best effectuates the purpose of the Act as explained in section III.C of this document. Accordingly, it is appropriate for the Agency to apply this longstanding concept of *active moiety* in determining the applicability of 5-year and 3-year marketing exclusivity for hyaluronidase products.

You are correct that Agency regulations at 21 CFR part 210 define the term *active ingredient* to mean the pharmacologically active component of a drug product.<sup>18</sup> However, the Agency has never applied the part 210 definition of active ingredient for purposes of interpreting the Act's 5-year and 3-year marketing exclusivity provisions. In fact, FDA has expressly declined to interpret *active ingredient* (including any ester or salt of the active ingredient) as meaning something other than active moiety (see 59 FR 50338 at 50358). Moreover, as explained in section IV.B, even if FDA analyzed these products on the basis of your preferred interpretation of this statutory language, your argument that Vitrase should not be treated as an NCE would still fail.

**B. 505(b)(2) Application Approval Does Not Require Demonstration of Sameness of Active Ingredient**

The Petition asserts that the Agency's approval of Vitrase under section 505(b)(2) of the Act demonstrates that Vitrase must contain a previously approved active ingredient, arguing that the Agency could not have approved a 505(b)(2) application for Vitrase otherwise. This is incorrect. As explained in section III.A, an applicant can rely on published reports of studies conducted by someone other than the applicant or on Agency findings of safety and effectiveness with respect to a previously approved product, to the extent such reliance is scientifically justified. The subsequent application need not be for a product containing the same active ingredient for such reliance to be scientifically justified. Neither section 505(b)(2) of the Act nor FDA's regulations expressly impose such a requirement; Agency guidance makes clear that we do not believe such a requirement exists, and the Agency has, in fact, approved 505(b)(2) applications for NCEs.<sup>19</sup>

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<sup>18</sup> The regulations at 21 CFR 210.3(b)(7) state that:

*Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

<sup>19</sup> See 21 U.S.C. 355(b)(2), 21 CFR 314.54(a), and the 505(b)(2) Response at 19-21. You note that the Agency's draft guidance for industry on *Applications Covered by Section 505(b)(2)* (Draft Guidance) recognizes 505(b)(2) of the Act as an appropriate vehicle for approval of naturally sourced and recombinant drug products for which clinical investigations "are necessary to show that the active ingredient is the same as the active ingredient in a listed drug." However, you take this statement out of context. The draft guidance does not state that a showing of sameness of active ingredient is required for approval of such a product. Rather, the language you quote comes from a description of one of the various types of applications that may be accepted through the 505(b)(2) pathway.

As discussed in section II, in the case of hyaluronidase, the Agency and applicants are justified in relying on a DESI determination, information derived from a long marketing history, and a body of literature describing studies on hyaluronidase from different mammalian sources, to support the safety and efficacy of certain hyaluronidase products for the currently approved uses, and in relying on a USP in vitro assay to determine that a particular product has sufficient enzymatic activity for the three currently approved indications. Because FDA and ISTA could rely on this information and experience, the Agency was able to approve Vitrase without requiring any long-term clinical studies, even though no hyaluronidase enzyme has yet been fully characterized. The sponsor had to demonstrate that Vitrase was sufficiently similar to the products considered in the DESI review, addressed in the marketing history, and described in the literature, to be able to rely on these sources of information for approval. This reliance did not require, however, that the Agency identify the *active ingredient* with chemical certainty. In short, the Agency did not need to conclude that Vitrase has the same active ingredient as a previously approved product to approve Vitrase using the 505(b)(2) pathway.

Certainly, any hyaluronidase product that – like Vitrase and Amphadase – relies on the Agency's DESI efficacy finding and the other safety and efficacy determinations discussed in section II must share certain characteristics with the drug products that formed the basis for all these determinations. As described in section II, these two products are, at least, members of the same general class of hyaluronidase products governed by the safety and effectiveness determinations made in the DESI review and by FDA. However, FDA does not have sufficient information to know if these products contain the same active moiety, which is why we are considering them each NCEs for exclusivity purposes.<sup>20</sup>

As this discussion makes apparent, hyaluronidase products fit into the regulatory frameworks for drug approval and marketing exclusivity in an unusual way.<sup>21</sup> Nevertheless, the Agency is using the standards and analytical approaches set out in the governing statutory provisions and our current regulations to address these products appropriately.

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<sup>20</sup> Accordingly, FDA currently would also be unlikely to consider these products to have the same active ingredient for purposes of approving an application under section 505(j) of the Act. More specifically, for example, it is unlikely that an applicant could obtain approval for an ANDA for a drug product containing a bovine or an ovine sourced hyaluronidase by citing Vitrase, with its incompletely characterized ovine sourced active ingredient, as its reference listed drug. In short, the active ingredient in Vitrase has not yet been sufficiently characterized to permit the Agency to conclude that another hyaluronidase product has an identical active ingredient (see 54 FR 28872 at 28881 (July 10, 1989) ("The [A]gency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean that the active ingredients must be identical")). In other words, the fact that different hyaluronidase products can be approved under section 505(b)(2) of the Act based on the DESI findings, applicable literature, information derived from marketing history and the in vitro assay does not mean that they *per se* have the same active ingredient for purposes of ANDA approval.

<sup>21</sup> The Agency assesses the similarity of drug products to make both drug approval and marketing exclusivity determinations. These two types of regulatory determinations are distinct and arise from different statutory and regulatory provisions (i.e., section 505(b)(1), (b)(2) and (j)(2) of the Act, and 21 CFR subparts B and C for approval; and section 505(c)(3)(E) and (j)(5)(F) of the Act, and 21 CFR 314.108 for 3-year and 5-year marketing exclusivity).

**C. A Presumption in Favor of NCE Status Will Not Produce Meaningless Exclusivity, Need Not Lead to Confusion, and Is Consistent with the Hatch-Waxman Objectives**

You state that the 5-year marketing exclusivity arising from the presumption in favor of NCE status may not provide meaningful protection to naturally sourced products containing proteins that have not been fully characterized and will lead to confusion. We do not agree.

The practical consequences of the presumption are clear and can be significant. If it is shown that a subsequent drug product includes an active moiety also included in the drug product entitled to exclusivity, acceptance of the subsequent application would be blocked for the duration of the exclusivity. If such a showing is not made, then the subsequent drug product would also be presumed to be an NCE. Its approval would not be blocked, and it would be eligible for its own 5-year marketing exclusivity that also would not block other approvals unless it is shown that a subsequent product contains an active moiety that is also present in the protected product.<sup>22</sup> This does not make the exclusivity meaningless. The exclusivity would, however, apply only to block subsequent products shown to contain an active moiety present in the protected product.

Further, the results of applying the presumption are consistent with the dual objectives of the Hatch-Waxman amendments, and you offer no arguments to the contrary. In enacting the Hatch-Waxman amendments, Congress struck a balance to promote two potentially competing policy goals: innovation and competition in the pharmaceutical marketplace (see, e.g., *Teva Pharmaceutical Industries Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005)). These goals inform Agency interpretation of the Hatch-Waxman amendments, including the exclusivity provisions. It is reasonable to expect the presumption of NCE status generally to have little effect on innovation while, at the same time, facilitating competition. In most cases, if it is not known whether a product contains a previously approved active moiety, each applicant seeking approval for the drug would face the same burden of having to submit its own NDA containing substantial clinical safety and effectiveness data, and each would receive 5 years of exclusivity. Each application would neither benefit from, nor delay the marketing of, any other.

The regulatory treatment of certain hyaluronidase products for their currently approved drug uses is unusual. However, application of the presumption in favor of NCE status to these products is consistent with the objectives of the Hatch-Waxman amendments as well. ISTA and Amphastar each sought and obtained approval, under section 505(b)(2) of the Act, for a mammalian testicular hyaluronidase product, Vitrase and Amphadase, respectively. As noted in section II, to obtain marketing approval for their NDAs, ISTA and Amphastar were able to rely almost entirely on existing literature and prior Agency findings, and each had only to conduct a small, short-term allergenicity study. These allergenicity studies were product-specific, meaning that the findings would not apply to hyaluronidase products from other manufacturers. Because the Agency did not have sufficient information to know whether these products contained any

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<sup>22</sup> In the event that such a showing can be made after a subsequent application has already been accepted for review, the Agency would have to determine how to apply the exclusivity. We have not yet been faced with this question and will not attempt to resolve it in the abstract here.

previously approved active moieties, both products received 5-year exclusivity in accordance with the presumption of NCE status. Subsequent applicants for similar hyaluronidase products for these uses would be expected to face similarly limited data requirements, as indicated in the Response to the Baxter Petition, and to receive 5-year marketing exclusivity if the presumption applies to them.

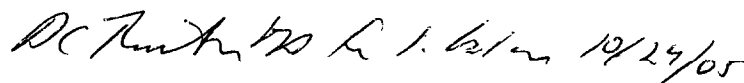
In short, granting NCE status to hyaluronidase products may result in multiple applicants who have filed similar 505(b)(2) applications (i.e., supported by the DESI findings, published literature, information derived from marketing history and product-specific in vitro activity and clinical safety data) obtaining approvals that are not delayed by the marketing exclusivity granted to any other product. This outcome would be consistent with the objectives of the Hatch-Waxman amendments, because it would promote competition without discouraging innovation.

You assert that disputes will arise regarding application of the presumption. This is certainly possible, as often is the case with regard to interpretation and application of the Hatch-Waxman amendments. However, we do not see this possibility as sufficient grounds for rejection of the presumption.<sup>23</sup>

#### **V. Conclusion**

FDA has the authority to apply a presumption in favor of statutory 5-year marketing exclusivity if the Agency has insufficient information to determine whether a product contains an active moiety approved in a previous application. For the reasons presented above, we continue to believe that FDA appropriately granted ISTA a 5-year period of marketing exclusivity for Vitrase. Accordingly, your petition is denied.

Sincerely,

A handwritten signature in black ink, appearing to read "DC [unclear] L. 1. 12/24/05".

Steven K. Galson, M.D., M.P.H.

Director

Center for Drug Evaluation and Research

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<sup>23</sup> You also argue that the Agency is determining exclusivity prospectively for all members of a class of drug products. That is not the case. Under this presumption, the Agency still determines exclusivity as part of the approval process for the specific application. We do not agree that the Act precludes the Agency from adopting an appropriate presumption that may be rebutted by product-specific evidence. Moreover, as eligibility for exclusivity depends in part upon what is known about the chemical composition of the drug product under review, the Agency's approach could place a premium on an applicant adequately characterizing its active ingredient to be able to identify the active moiety. This additional pharmaceutical characterization would be useful information for drug development and the public health.